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Overview and SWOT analysis of nano-ferroptosis therapy for cancers†

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Cancer remains one of the leading causes of death worldwide. In the search for effective treatments, conventional therapies such as chemotherapy, radiotherapy, and immunotherapy have emerged as mainstream options. However, these therapies often come with significant side effects, resulting in unsatisfactory treatment outcomes. In contrast, the emerging field of nano-ferroptosis therapy has considerable promise for cancer treatment, offering notable advantages in tumor targeting, mitigating drug resistance, and minimizing toxicity. Nano-ferroptosis therapy leverages nanocarriers with high loading capacities and structural tunability to deliver ferroptosis inducers, thereby inhibiting tumor growth through mechanisms such as the enhanced permeability and retention effect or active targeting for precise delivery to the tumor site. This review outlines the current status of research on nano-ferroptosis therapy for various cancer types, with a focus on four key aspects: strengths, weaknesses, opportunities, and threats (SWOT). Based on these insights, we propose recommendations and solutions for each aspect of the SWOT analysis. It is expected that this review will provide some insights for advancing nanomedicine design, deepening our understanding of ferroptosis mechanisms, and guiding the development of more effective strategies for cancer treatment.

1. Introduction

Cancer is a chronic disease characterized by high morbidity and mortality, making it the second leading cause of death after cardiovascular disease.[1] The incidence and mortality rates of cancers are shown in Fig. S1 (ESI†). Treating cancer imposes a considerable financial burden on society. For example, Chen *et al.* predict that the global economic cost of cancer will reach $ 25.2 trillion globally from 2020 to 2050.[2] Consequently, achieving more efficient and effective anti-cancer treatments remains a focal point of current research.

To address these challenges, scientists, in collaboration with clinicians, have developed various anti-cancer therapies, including surgery,[3] radiotherapy,[4] chemotherapy,[5] immunotherapy,[6] chemodynamic therapy,[7] photothermal therapy,[8] and palliative care.[4] However, each of these anti-cancer therapies presents certain drawbacks and risks. For example, surgical procedures may lead to many complications such as infection and bleeding, with a high risk of cancer recurrence.[9] Radiotherapy, chemotherapy, and immunotherapy can cause damage to healthy organs or tissues, introduce potential toxicity, and even promote drug resistance in cancer cells.[10–12] Chemodynamic and photothermal therapies suffer from poor targeting and low therapeutic efficiency.[13] Additionally, palliative care is associated with high costs and lacks a clearly defined specialized care pathway.[14] Confronting these drawbacks, some emerging therapies, such as nano-ferroptosis have garnered increasing attention for their potential effectiveness.

As suggested by its name, nano-ferroptosis therapy encompasses two interrelated components: nanocarriers and ferroptosis. This section introduces the therapy from these two aspects. Ferroptosis is a recently discovered iron-dependent regulatory cell death, characterized by the accumulation of intracellular lipid peroxide (LPO).[15] This process can inhibit the growth of a wide range of tumors. Studies have reported that drug-resistant cancer cells, especially those that metastasize readily, are more susceptible to undergoing ferroptosis.[16] The main pathways by which ferroptosis eliminates tumor cells include: (1) abnormal iron metabolism, (2) imbalance of the amino acid antioxidant system, and (3) lipid peroxidation. Key regulators of the abnormal iron metabolism pathway include transferrin receptor 1 (TfR1), STEAP family member 3 (STEAP3),[17] divalent metal transporter protein 1 (DMT1),[18] and nuclear receptor coactivator 4 (NCOA4).[19] The main substances that play a role in the imbalance of the amino acid antioxidant system pathway are system Xc^-, glutathione (GSH), and glutathione peroxidase 4 (GPX4).[20] Finally, the main components regulating the lipid peroxidation pathway include Acyl-CoA synthetase long-chain family member 4 (ACSL4),

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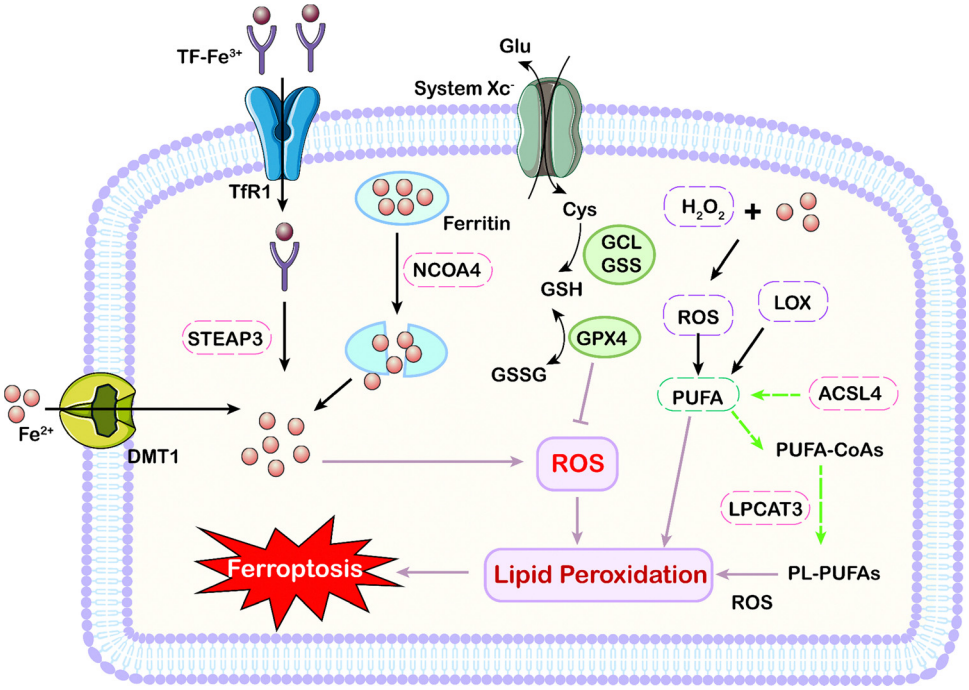

Fig. 1 Schematic diagram of the ferroptosis pathway. Abbreviations: TfR1: transferrin receptor 1, STEAP3: STEAP family member 3, DMT1: divalent metal transporter protein 1, NCOA4: nuclear receptor coactivator 4, Glu: glutamate, Cys: cysteine, GSH: glutathione, GCL: glutamate–cysteine ligase, GSS: glutathione synthase, GPX4: glutathione peroxidase 4, GSSG: oxidized GSH, H_2O_2: hydrogen peroxide, PUFA: polyunsaturated fatty acid, ACSL4: Acyl-CoA synthetase long-chain family member 4, LPCAT3: lysophosphatidylcholine acyltransferase 3, LOX: lipoxygenase, ROS: reactive oxygen species.

lysophosphatidylcholine acyltransferase 3 (LPCAT3),[21] and lipoxygenase (LOX).[22] The specific regulatory process is shown in Fig. 1.

Ferroptosis can be modulated by either inhibiting or activating the abovementioned pathways. Furthermore, tumor therapy requires the activation of ferroptosis to kill tumor cells. Administration of ferroptosis inducers is a common method to induce ferroptosis in tumor cells.[23] However, most ferroptosis inducers suffer from low water solubility and poor bioavailability, and their druggability is far from satisfactory.[24] To address these limitations, scientists typically utilize nanocarriers to encapsulate these inducers, thereby formulating nanomedicines (Fig. 2) for the nano-ferroptosis therapy.[25] Nanoparticles play a significant role in various medical applications due to their wide range of functions, such as enhancing drug targeting, reducing drug resistance, and minimizing adverse effects, including the diagnosis and treatment of diseases, which is a powerful aid in the process of treating cancer by applying ferroptosis. Firstly, it can be used as an excellent drug carrier to deliver ferroptosis inducers. Some organic nanocarriers with good biocompatibility, such as liposomes, polymer nanocarriers, micelles, *etc.*, can encapsulate the toxic or insoluble inducers inside them to improve the solubility and stability of the drugs and to reduce their systemic toxicity. Nanocarriers with surface-modified ligands can precisely deliver their loaded drugs to tumor sites and be taken up by tumor cells.[26] Stimuli-responsive nanocarriers that respond to specific exogenous or endogenous stimuli, including ionizing radiation-responsive, ultrasound-responsive, GSH-responsive, pH-responsive, and

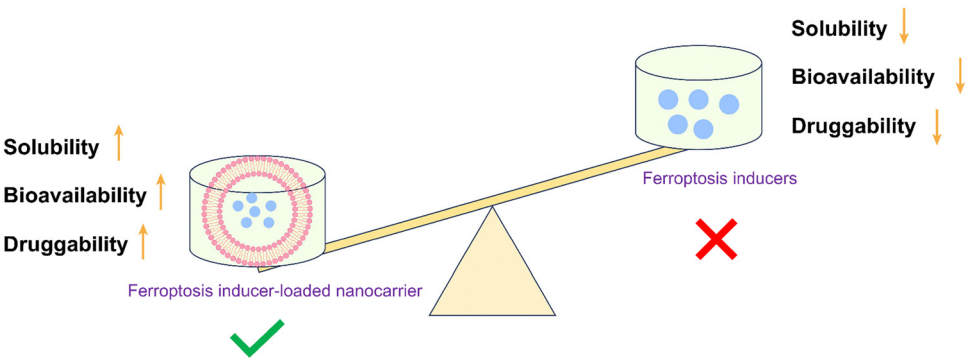

Fig. 2 Schematic representation of ferroptosis inducer-loaded nanocarriers.

glucose-responsive nanocarriers, can be used to flexibly control the release of drugs and increase drug accumulation at the lesion site.[27] Exceptionally, polymeric nanocarriers with amphiphilic properties enable combined therapy of ferroptosis with other cell death modalities to kill tumors through multiple pathways and ensure high drug loading rates and low side effects.[27] In addition, nanoparticles can also directly induce ferroptosis. For example, iron-based nanomaterials can increase the intracellular iron content and disrupt the oxidative equilibrium within the cell using the Fenton reaction, thereby inducing ferroptosis.[28] Non-iron-based nanomaterials such as manganese dioxide nanoparticles themselves can deplete intracellular GSH and effectively increase intracellular oxygen species (ROS) levels, ultimately leading to excessive accumulation of lipid peroxides, which in turn induce ferroptosis in tumor cells.[29] Finally, nanoparticles can also regulate the tumor microenvironment by increasing the oxygen content and decreasing the acidity in tumor tissues, which in turn enhances the therapeutic effect of ferroptosis. For example, a polypyrrole nanoparticle containing iron ions prepared by Cui *et al.* possessed hydrogen peroxide (H_2O_2)-like enzyme activity, which could decompose intracellular H_2O_2 to generate $^{\bullet}OH$, thereby alleviating tumor hypoxia and promoting vascular normalization of the tumor microenvironment.[30] Another similar study by Dong *et al.* proposed a nanosystem loaded with perfluorocarbons PFCE. The PFCE was highly efficient in carrying oxygen, which enabled the nanoparticles to function as long-circulating oxygen carriers to regulate the tumor hypoxic environment. In addition, the nanosystem can alleviate the acidic microenvironment of tumors by regulating glucose metabolism, inhibiting lactate production, and neutralizing protons.[31] In summary, the integration of nanomedicine with ferroptosis therapy has the potential to yield remarkable effects. In other words, nano-ferroptosis therapy has significant promise for advancing cancer treatment.

Although the abovementioned advantages of nano-ferroptosis therapy are promising, no product has yet reached the market. Consequently, it is imperative to understand both the potential and challenges associated with this therapy to accelerate the foundational research, facilitate practical applications, and initiate clinical trials. This review will briefly describe the current state of nano-ferroptosis cancer therapy (located in the ESI†) and employ SWOT analysis to analyze the strengths, weaknesses, opportunities, and threats of this therapy, thereby identifying future directions. We anticipate that this review will provide insights for advancing nanomedicine design and elucidating the mechanism of ferroptosis in oncology. Additionally, it aims to provide strategic guidance for the development of innovative and effective cancer therapies.

2. *Status quo* of research on nano-ferroptosis therapy for cancers

2.1 Ferroptosis inducers

Ferroptosis inducers can interfere with iron, lipid, and ROS metabolism in cancer cells, and also upregulate tumor suppressor genes that can directly promote ferroptosis in cancer cells. Commonly used ferroptosis inducers include system Xc^--inhibitors (erastin, piperazine erastin, imidazole ketone erastin, sorafenib (SRF), sulfasalazine (SAS)), GPX4-inhibitors (RSL3, ML210, FIN56, artesunate (ART)), thioredoxin (TXN) inhibitor (ferroptocide and the fluorescent ferroptocide derivative P30), GSH-inhibitors (cisplatin, dihydroartemisinin (DHA)), and iron activators (neratinib, salinomycin, FINO2).[32,33] The chemical structures of these compounds are shown in Fig. 3.

The pharmacologic effects of various ferroptosis inducers have been extensively investigated. For example, Wei *et al.* demonstrated that erastin significantly inhibited the invasion, colony formation, and migration of HeLa and SiHa cells, with a half maximal inhibitory concentration (IC50) of 30.88 μM for HeLa and 29.40 μM for SiHa cells.[34] In another study, Kim *et al.* showed that SRF inhibited the growth of NCI-N87 cells in a concentration-dependent manner, with an IC50 of approximately 16.345 μM.[35] In addition, Gout *et al.* reported the inhibitory effect of SAS on lymphoma growth and demonstrated that SAS exhibited high *in vitro* inhibitory activity against rat lymphoma, with an IC50 of 160 μM.[36] GPX4 inhibitors induce ferroptosis by inhibiting the activity of GPX4 against lipid peroxidation, leading to the accumulation of LPO in cancer cells. Asperti *et al.* compared the susceptibility of two HCC cell lines, Hepg2 and HA22T/VGH, to RSL3-induced ferroptosis, revealing that highly differentiated Hepg2 cells (IC50 = 0.07 μM) were more susceptible to ferroptosis than low-differentiated HA22T/VGH cells (IC50 = 0.3 μM).[37] Similarly, Wang *et al.* found that ML210 had a significant tumor growth inhibitory effect on HT1080 cells with an IC50 value of 0.1 μM.[38] Additionally, it has been reported that FIN56 greatly reduced the cell viability of two GBM cell lines, LN229 and U118 cells, with IC50 values of 4.2 μM and 2.6 μM, respectively, as well as inhibiting cancer cell proliferation and inducing ferroptosis *in vivo*.[39] Li *et al.* demonstrated that ART, when combined with oligonucleotide conjugate (SAC), exhibited high toxicity toward CEM and HCT116 cell lines, with an IC50 of 57.8 nM for HCT116 cells and 33.04 nM for CEM cells.[40] Cisplatin and DHA also induce ferroptosis by inhibiting GSH synthesis in cancer cells, while their toxic effects on cancer cells should not be underestimated. For example, cisplatin exhibited IC50 values of 4 μM and 7 μM against the SW620 and SKOV3 cell lines, respectively.[41] For DHA, the IC50 values were 19.68 μM and 7.08 μM against lung cancer cell lines PC9 and NCI-H1975, respectively.[42] Similar studies have also shown that neratinib an iron activator has an IC50 value of approximately 0.014 μM for HER2/neu amplified sarcoma cell lines, compared to 0.164 μM for non-HER2/neu amplified sarcoma cell lines, suggesting greater sensitivity in HER2/neu amplified cell lines.[43] Salinomycin exhibited a significant inhibitory effect on melanoma cells, with an IC50 value of 0.82 ± 0.60 μM against SK-Mel-19 melanoma cells.[44] Additionally, FINO2 reduced the viability of bile duct carcinoma (BTC) cell lines, with IC50 values ranging from 3.2–50 μM.[45] In conclusion, the pharmacological effects of various ferroptosis inducers play a critical role in inducing ferroptosis and effectively killing cancer cells.

2.2 Nanocarriers

The nanocarriers commonly used in nano-ferroptosis therapy include dendrimers, polymeric micelles (PMs), mesoporous

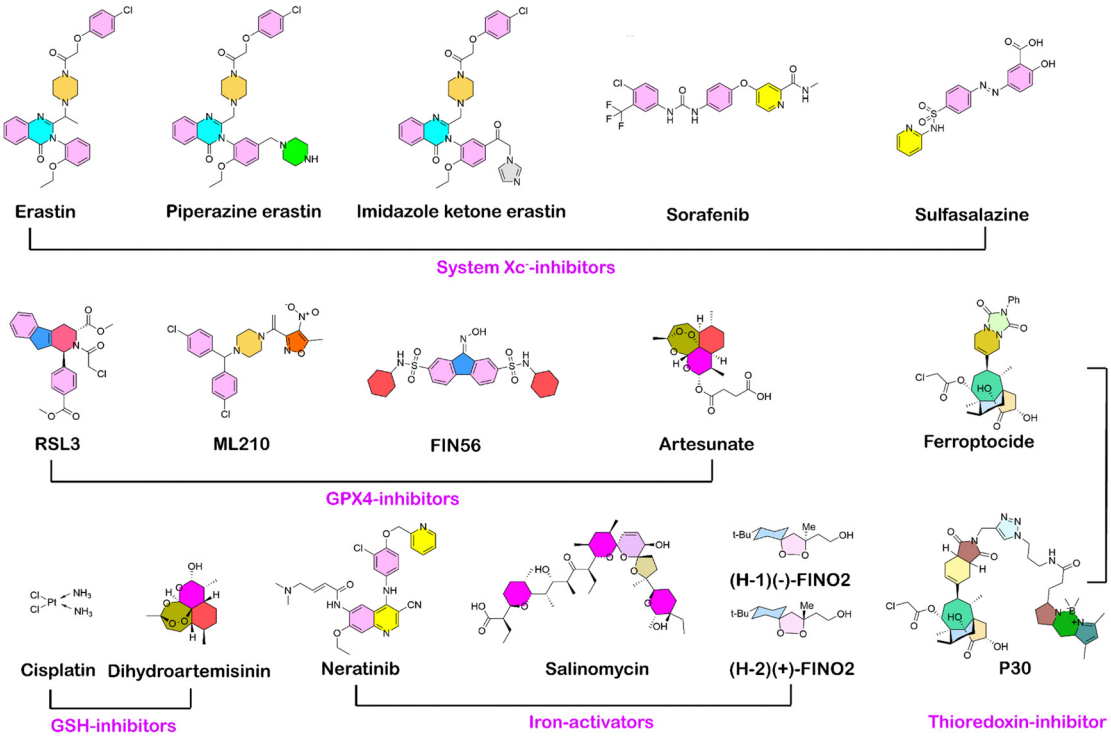

Fig. 3 Chemical structure of representative ferroptosis inducers.

silica nanoparticles (MSNs), liposomes, nanozyme, and iron oxide nanoparticles (IONPs)[46] (Fig. 4).

In the application of ferroptosis for cancer treatment, nanocarriers play an important role in improving the efficiency of drug delivery. For example, Salimi *et al.* evaluated the role of polyamidoamine (PAMAM) dendrimer-coated iron oxide nanoparticles (G4@IONPs) in inhibiting tumor growth in BALB/c mice. The study showed that PAMAM as a coating for IONPs significantly improved the efficiency of drug delivery by postdecreasing their uptake in the reticuloendothelial system (RES) organs and prolonging blood circulation time.[47] Furthermore, Liu *et al.* designed a PM loaded with the ferroptosis inhibitor curcumin, and the results showed that the constructed micellar drug delivery system could significantly improve the water solubility and bioavailability of curcumin and enhance the antitumor activity of the drug.[48] In another study, a new generation of hollow mesoporous silica nanoparticles (HMSNs) exhibited excellent doxorubicin (DOX) loading efficiency and intelligent drug release *via* a triple reaction triggered by GSH/pH/near-infrared (NIR) irradiation, resulting in improved chemotherapeutic efficiency and enhanced ferroptosis.[49] Similarly, Luo *et al.* developed a ROS-responsive liposome based on borate-caged phosphatidylcholine, where responsive drug release occurred at high ROS levels in the tumor microenvironment, significantly increasing drug accumulation at the tumor site.[50] Moreover, a biomimetic hybrid nanoenzyme system (M@GOx/Fe-HMON) consisting of hollow mesoporous organosilica nanoparticles (HMONs) and homologous tumor cell membranes was reported for co-loading GOx and Fe to induce ferroptosis. The homologous cell membrane homing effect therein significantly enhanced the tumor targeting of M@GOx/Fe-HMON, which in turn improved the anticancer effect.[51] Finally, the study of Wu *et al.* demonstrated that hyaluronic acid (HA)-coated siProminin2-loaded FeOOH nanoparticles (FeOOH/siPROM2@HA) were able to specifically target mammary CSCs and release the drug in the acidic environment of the tumors, resulting in an increase in iron content, thus inducing ferroptosis.[52] In summary, nanocarriers play a pivotal role in enabling efficient, targeted nano-ferroptosis therapy for cancer treatment.

3. SWOT analysis

SWOT analysis is a strategic planning tool that aids decision-makers in clarifying their direction by systematically evaluating an item's internal strengths and weaknesses, as well as external opportunities and threats. This approach helps optimize resource allocation to adapt to a changing environment. While initially employed in marketing, SWOT analysis has since found applications in the biomedical field. For instance, Zhang *et al.* comprehensively explored the potential advantages and challenges of nanomedicine by using the SWOT analysis framework to assess the feasibility of its clinical translation. The analyses highlighted that although nanomedicine has great potential for applications in areas like drug delivery, biosensing, and regenerative medicine, it also faces significant challenges, such as safety, the feasibility of scaling up, and exorbitant cost.[53] These insights have informed subsequent research in the field. In addition, Duo *et al.* applied SWOT

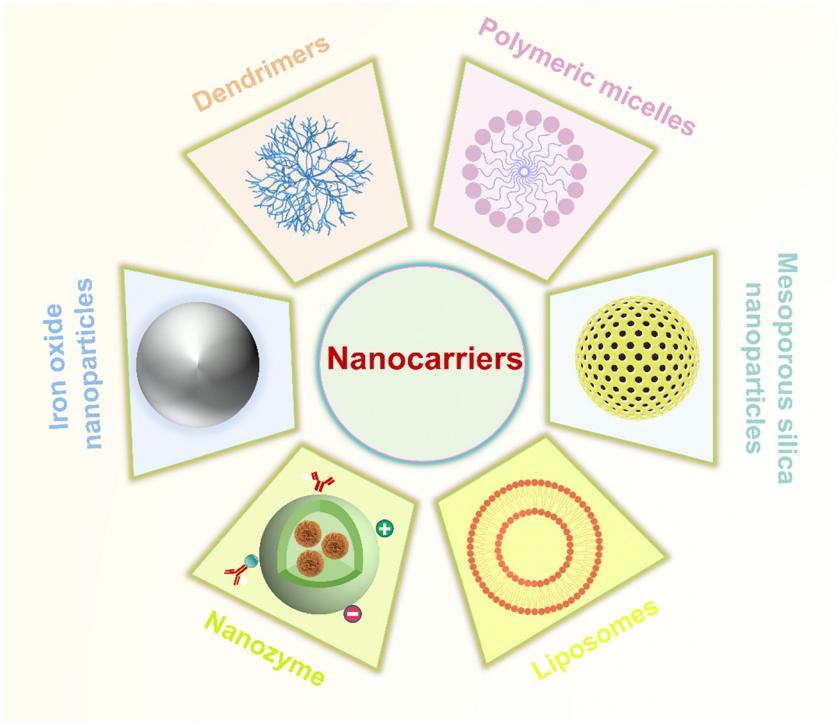

Fig. 4 Different nanocarriers for nano-ferroptosis therapy.

analysis to evaluate the current challenges and future opportunities for borophene-based nanomedicines in cancer therapy.[54] Similarly, Giusti *et al.* employed SWOT analysis to investigate the applicability and effectiveness of policies/programs across European countries aimed at tackling non-communicable diseases, such as diabetes. This study provided valuable insights from different nations, aiding policymakers in making more informed and timely decisions.[55]

Given that there are no marketed products for nano-ferroptosis therapy, there is a pressing need to apply SWOT analysis to summarize strategies that can guide ongoing basic research, application development, and clinical trials. Through a comprehensive literature survey conducted using databases such as PubMed, Web of Science, and Scopus, we have compiled key insights on the four aspects of strengths, weaknesses, opportunities, and threats. The SWOT analysis of nano-ferroptosis therapy is summarized in Fig. 5 and described below.

3.1 Strengths

The advantages of nano-ferroptosis therapy are significant and multifaceted, encompassing tumor targeting, mitigating drug

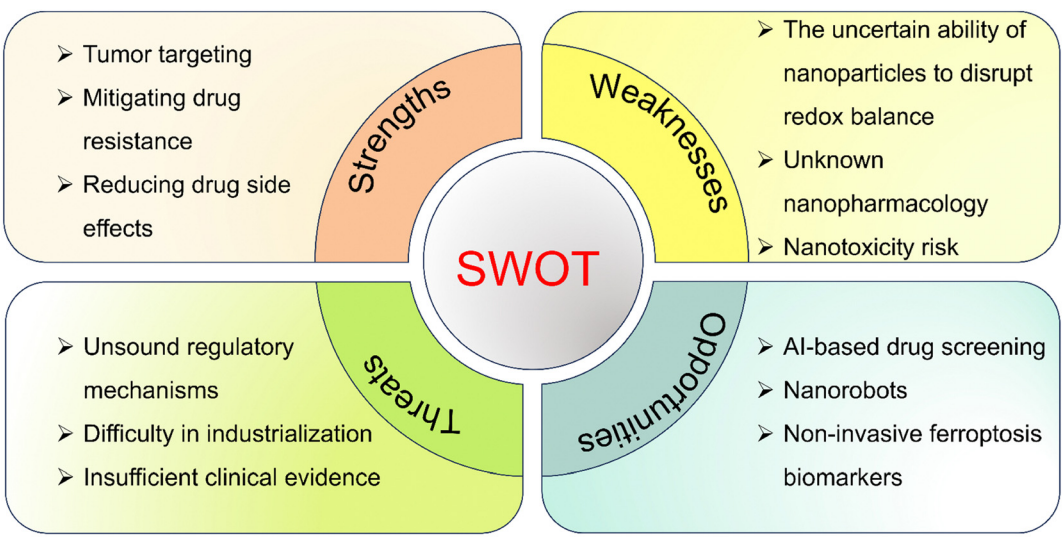

Fig. 5 SWOT analysis of nano-ferroptosis therapy for cancers.

resistance, and reducing drug side effects. These benefits will be explained in turn.

3.1.1 Tumor targeting. Achieving precision cancer treatment has been a major focus of research. Over the past few decades, scientists have developed various targeted delivery methods to improve cancer therapy. However, a significant challenge to the success of targeted therapy is poor therapeutic targeting, which leads to severe damage to normal tissues. This challenge also applies to the delivery of ferroptosis inducers. Nanoscale drug delivery systems can overcome these challenges by targeted design.[56] These strategies are typically categorized into active and passive targeting. Active targeting strategies, also known as ligand-mediated targeting, utilize the physicochemical properties of the nanocarrier surface, biological interactions (affinity ligands), and response to various stimuli to recognize specific receptors or antigens on the target cells. This strategy increases cellular uptake by the target cells, thereby improving the therapeutic efficacy.[57] In contrast, passive targeting strategies rely on the enhanced permeability and retention (EPR) effects, which enable selective accumulation of drug-loaded nanoparticles at the tumor site.[58] Both strategies play crucial roles in the cancer treatment process.

Nano-ferroptosis therapy can amplify ferroptosis by employing nanocarriers with high targeting capacity, thereby fulfilling the requirements of precision cancer treatment. Li *et al.* developed magnetically responsive nanoparticles (MNPs) capable of precise treatment of GBM by targeting low-density lipoprotein receptor-related-1 protein (LRP-1), which is overexpressed in GBM. These MNPs consisted of magnetic Fe_3O_4 NPs coated with mesoporous SiO_2 and brequinar (BQR, an FDA-approved dihydro nicotinic acid dehydrogenase (DHODH) inhibitor), conjugated with angiopep-2 (ANG) peptide-modified exosome (ANG-EXO) to form a functionalized nanoparticle. The MNPs induced ferroptosis by catabolizing DHODH, an enzyme essential for tumor cell proliferation, and by depleting GPX4 in mitochondria. In addition, small interfering RNA of GPX4 (siGPX4) was encapsulated in exosomes, and the two components were bound together by antigen–antibody interactions. Finally, ANG-EXO-bound MNPs successfully crossed the blood–brain barrier (BBB) and specifically targeted GBM cells in the presence of ANG, while BQR is released in the TME. The results showed that A172 and LN229 cells showed stronger uptake of ANG-EXO, with an approximately 3-fold increase in uptake rate, compared to non-targeted peptide exosomes and normal exosomes. Further studies showed that the fluorescence intensity in the brain tumor region was significantly stronger in the MNP@ANG-EXO-treated samples. Consequently, the ANG-EXO conjugated MNPs within the TME exerted a combined therapeutic effect on GBM cells by degrading DHODH, selectively delivering siGPX4, and releasing Fe^{2+} to trigger the Fenton reaction, as shown in Fig. 6.[59] Similarly, Wang *et al.* developed a multifunctional nanomedicine delivery system (GDYO@SP94/DOX-Fe^{2+}/sorafenib/SLC7A11-i), denoted as MNMG, for targeted HCC delivery. This system was based on the co-assembly of therapeutic drugs and short peptides with targeted effects. Interestingly, each component of the system played a distinct role, culminating in a synergistic and efficient tripartite approach to treating HCC. The results showed that mice treated with MNMG@Cy5.5 exhibited significant Cy5.5 fluorescence at the tumor site, indicating that MNMG could accumulate at the tumor site through the EPR effect and sustainably induce ferroptosis of tumor cells, with potent inhibitory effects on the proliferation, migration, and invasion of HCC cells.[60] In addition, Lim *et al.* developed a novel nanosystem, NP + NP, by combining protamine nanoparticles (PPNC NPs) loaded with negatively charged curcumin (NCur) and heparin-based nanoparticles (HDFe NPs) encapsulating doxorubicin and Fe^{3+}. The results demonstrated that the fluorescence intensity in the tumor tissues of the NP + NP-treated group was 3.64-fold higher compared to the control group, indicating that the NP + NP system had strong targeting properties and significantly inhibited tumor growth.[61]

3.1.2 Mitigating drug resistance. Drug resistance remains a significant challenge in cancer treatment, categorized into primary and secondary types. The molecular mechanisms underlying chemotherapy resistance mainly include decreased drug activity, reduced drug uptake, and escape from apoptosis.[62] Studies have shown that a high mesenchymal cellular status in cancer cell lines contributes to resistance to therapeutic modalities. However, this mesenchymal resistance status depends on the expression of intracellular antioxidant systems (mainly GSH and GPX4). Accordingly, the drug-resistant status of cancer cells can be altered by down-regulating GSH levels and inhibiting GPX4 activity, enhancing the sensitivity of cancer cells to therapeutic drugs by inducing ferroptosis.[63] In addition, nanoparticles play an important role in mitigating drug resistance.[64]

Many studies have explored the use of nano-ferroptosis therapy to reduce drug resistance in cancer cells. For example, Zhu *et al.* developed GSH-triggered nanolocks (MTO–Cu(II)–cRGD) with active tumor targeting capability. In MTO–Cu(II)–cRGD, copper(II) served as an inducer for the chemotherapeutic drug mitoxantrone (MTO), and the two components form a metal–organic coordination compound. Upon entering the high GSH environment of the tumor, Cu(II) in the nanolocks was reduced to Cu(I), leading to the decomposition of the ligand structure and releasing the encapsulated drug. This process led to the accumulation of LPO within the cells, ultimately inducing ferroptosis. In this study, the authors constructed a cellular resistance model to investigate how MTO–Cu(II)–cRGD could reverse chemoresistance. The results showed that GSH and GPX4 contents in cells were significantly up-regulated by MTO treatment, but were inhibited by MTO–Cu(II)–cRGD treatment. Moreover, the down-regulation of drug-resistant protein expression P-glycoprotein (P-gp) in cancer cells after MTO–Cu(II)–cRGD treatment also validated that the nanolock MTO–Cu(II)–cRGD effectively prevented the formation of chemoresistance.[65] Similarly, Wang *et al.* designed a nanocatalytic sensitizer (VF/S/A@CaP), co-loaded with Vc–Fe(II), otubain-2 (OTUB2)-siRNA (si-OTUB2), and long noncoding RNA metastasis-associated lung adenocarcinoma transcript1 (ASO-MALAT1) for the treatment of osimertinib (AZD9291)-resistant NSCLC. Both *in vivo* and *in vitro*

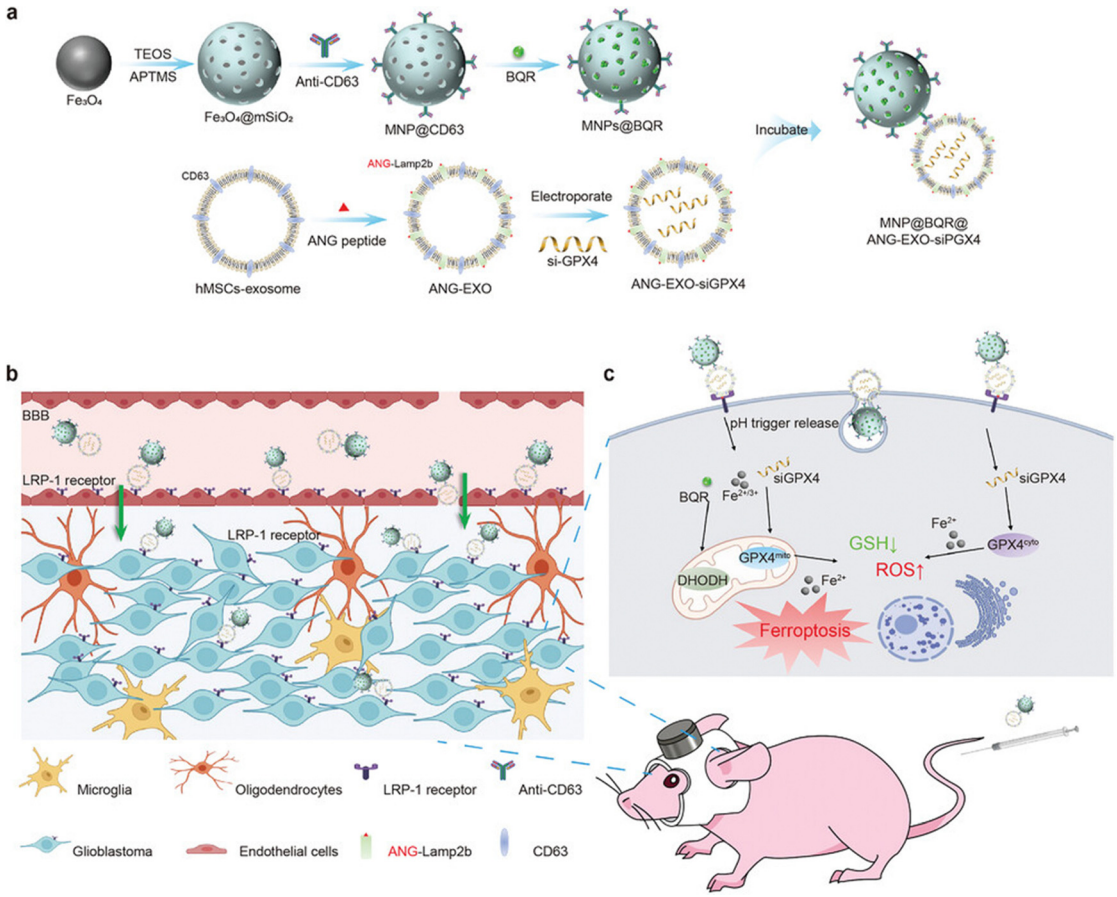

Fig. 6 Ferroptosis induction platform for magnetic targeting and drug delivery using MNPs. (a) Schematic illustration of the design and synthesis of MNP@BQR@ANG-EXO-siGPX4. (b) Schematic of the magnetic mouse helmet and the mechanisms by which the ANG peptide-mediated NPs crossed the BBB to accumulate in tumors. (c) The mechanism underlying the induction of GBM cell ferroptosis. Reproduced from Li *et al.* with permission from the Advanced Science.[59] Abbreviations: BQR: brequinar, ANG: angiopep-2, hMSCs: human mesenchymal stem cells, EXO: exosome, GPX4: glutathione peroxidase 4, siGPX4: small interfering RNA of GPX4, LRP-1: lipoprotein receptor protein 1, DHODH: dihydroorotate dehydrogenase, MNPs: magnetic nanoparticles, GSH: glutathione, ROS: reactive oxygen species.

studies demonstrated that VF/S/A@CaP induced ferroptosis by cyclically depleting GSH thereby in drug-resistant cancer cells. Furthermore, experiments exploring the sensitivity of drug-resistant cancer cells to ferroptosis revealed that AZD9291-resistant tumor cells exhibited higher sensitivity to ferroptosis than AZD9291-sensitive tumor cells when treated with Vc and Fe(II). These findings indicated that VF/S/A@CaP mitigated the therapeutic drug resistance in cancer cells by inducing ferroptosis, significantly enhancing treatment efficacy against drug-resistant tumor cells.[66] In a related study, Guan *et al.* developed a multimodal drug delivery nanoplatform with ROS cascade amplification (TK-Fc/LAE NPs) using the diblock polymer PTKPTX-*b*-PFc (TK-Fc) and the stabilizer lauryl arginine ethylester (LAE). The nanoplatform exerted its therapeutic effects through three main pathways: (1) reversal of MDR by inhibiting P-gp expression and mitochondrial function, (2) induction of ferroptosis *via* ferrocene, and (3) reduction in the systemic toxicity by precisely controlling the release of the chemotherapeutic drug PTX. Studies showed that the TK-Fc/LAE NP group had the strongest effect in reducing mitochondrial membrane potential (MMP) and ATP levels, thereby inhibiting P-gp function and mitigating drug resistance in cancer cells. This gas therapy/ferroptosis/chemotherapy trinity of multimodal nanoplatforms had a synergistic therapeutic effect on tumor cells and shows promise as an emerging strategy to reverse MDR.[67]

3.1.3 Reducing drug side effects. In conventional cancer treatments, such as chemotherapy and radiotherapy, toxic side effects are a significant concern. Although emerging ferroptosis therapies can mitigate cancer cell resistance and strongly inhibit the growth and metastasis of tumor cells, the ferroptosis inducers are not without toxicity. These inducers can cause damage to healthy organs or tissues, especially when used in combination with other treatment. However, nanocarriers can specifically deliver the encapsulated drug to the lesion site due to their excellent spatial controlled release properties. This localized delivery reduces the risk of premature drug leakage, thereby minimizing the damage to surrounding healthy organs or tissues. Besides, nano-delivery systems can lower the required dose and frequency of drug administration, further mitigating the toxic side effects associated with large drug accumulations.[68] Therefore, nano-ferroptosis therapy, which leverages nanocarriers to deliver ferroptosis inducers, has

garnered widespread attention for its ability to reduce the systemic toxicity and improve the safety of cancer treatment.

Recently, a composite therapeutic biomimetic nanoplatform (MPDA/Fe/RSL3@M-gy1), constructed using a genetic engineering strategy to enhance the therapeutic efficacy and safety of prostate cancer (PCa), was reported. The mediator pore polydopamine (MPDA) served as the drug-carrying core. PSMA, a transmembrane glutamate carboxypeptidase overexpressed in PCa cells, acted as the therapeutic target. The gy1 antibody fragment, was a PSMA-specific single-chain antibody, was employed on the membrane for active targeting. Results revealed that RSL3 alone was cytotoxic to both the normal human liver cell line MIHA (IC50 = 2.169 μM) and human kidney cell line HK-2 (IC50 = 1.118 μM). In addition, iron ions inhibited the growth of CRPC cells (IC50 = 1066 μM and 804.6 μM), but also caused indiscriminate damage to normal liver and kidney cells (IC50 = 380.2 μM and 345.8 μM). Notably, MPDA-based nanostructures were found to be non-toxic, indicating that encapsulation of Fe/RSL3 in nanoparticles can help mitigate potential toxic side effects. In summary, the MPDA/Fe/RSL3@M-gy1 nanoplatform demonstrated significantly improved efficacy and safety, with robust targeting of PCa tumors and ferroptosis induction.[69]

In addition to the safety risks of ferroptosis inducers, the toxic side effects of other auxiliary drugs, such as chemotherapeutics, should not be underestimated. These drugs are typically co-delivered with ferroptosis inducers to enhance the anticancer efficacy. Therefore, minimizing the potential toxicity of chemotherapeutic agents is a critical consideration when designing cancer treatment programs. To address this challenge, Sun *et al.* developed a multifunctional nanosystem (ODLP-PEGH8 NPs) that combines chemotherapy, photothermal therapy, and immunotherapy for breast cancer treatment. A key innovation of this nanosystem was the surface modification with a pH-responsive functional peptide, PEGH8. This modification enabled enhanced cellular uptake through charge flipping induced by the tumor microenvironment, while also facilitating intracellular lysosomal escape. Furthermore, lapatinib (LTB), which induces ferroptosis and leads to intracellular accumulation of iron ions resulting in toxicity, and the chemotherapeutic drug oxaliplatin (OXA), known for its gastrointestinal toxicity, exhibited significant safety improvements when delivered *via* nanocarriers. Specifically, when both drugs were loaded into ODLP-PEGH8 NPs, the nanoplatform mitigated their inherent toxicities. No significant pathological necrosis and inflammatory lesions were observed in otherwise healthy tissues after treatment with ODLP-PEGH8 NPs. However, focal metastases were observed in all groups of hormonal mice, except those treated with ODLP-PEGH8 NPs. Ultimately, ODLP-PEGH8 NPs demonstrated highly efficient anti-tumor activity, excellent biological safety, and easy degradability *in vivo*.[70] Similarly, Lin *et al.* developed polymer nanoparticles (mPEG-*b*-PPLGFc@Dox) to reduce the toxicity of the chemotherapeutic drug DOX. *In vivo* safety studies revealed that while free DOX caused significant cardiotoxicity and nephrotoxicity, the use of mPEG-*b*-PPLGFc@Dox nanoparticles showed no significant differences in cell morphology, histological structure, and serum biochemical indexes of normal organs compared to the control group. This indicated that the use of nanocarrier-encapsulated DOX significantly reduced the systemic toxicity and side effects of DOX.[71]

In conclusion, nano-ferroptosis therapy offers numerous advantages, including enhanced targeting capabilities, mitigation of cancer cell resistance, and reduced drug-induced side effects. With its great potential in treating various cancers, it is crucial to fully harness the advantages of nano-ferroptosis therapy to improve the efficiency of anti-cancer treatments.

3.2 Weaknesses

The weaknesses of nano-ferroptosis therapy include challenges such as the uncertain ability of nanoparticles to disrupt redox balance, unknown nanopharmacology, and the potential risk of nanotoxicity, which will be discussed in detail below.

3.2.1 The uncertain ability of nanoparticles to disrupt the redox balance. The main factor driving ferroptosis in tumor cells is the excessive accumulation of LPO, with the key determinant being the activity of the cellular antioxidant system. When this defense system is inactivated, LPO levels increase, promoting ferroptosis. However, the presence of a robust antioxidant system in cancer cells can significantly reduce the effectiveness of cancer treatment, making them less effective in certain tumor types. Antioxidant systems typically include GSH, selenium, and the coenzyme Q (CoQ) system. When ferroptosis therapies are used to treat cancer, the antioxidant system in cancer cells can counteract the treatment by defending against ferroptosis, reducing the therapy's effectiveness. These systems may act individually or in concert, creating a more robust defense.

Although nanoparticles can disrupt the cellular antioxidant system to a certain extent, differences in uptake efficiency of tumor cells, complex intracellular environments, and difficulties in releasing the drug precisely as designed can greatly diminish the effect of nanoparticles. Consequently, the antioxidant system will still exert a strong resistance during treatment, weakening the therapeutic effect. Internalization of nanoparticles is a crucial process for the precise delivery of drugs to their intracellular targets, and intracellular nanoparticle exposure correlates strongly with the antitumor efficacy of nanomedicines.

However, tumors are heterogeneous, as evidenced by large differences in nanoparticle uptake efficiency among different tumor cells and even among individuals of the same tumor cell type. Yin *et al.* found that only 20% of tumor-accumulating nanoparticles were taken up by tumor cells and related cells, while about 80% of nanoparticles were isolated in cell-free areas of the tumor.[72] The complex tumor microenvironment can act as a powerful security system that automatically activates protective mechanisms to protect solid tumors from ''intruders'' when they are detected, thereby maintaining intracellular redox balance. For example, small extracellular vesicles secreted by tumor cells act as a ''force field'' to intercept nanoparticles, which are then transferred to the liver for

degradation and metabolism, thus impairing the effects by nanoparticles.[73] The above facts imply that nanoparticles may not be able to fully enter tumor cells to play a role in disrupting the antioxidant system, limiting their ability to regulate the overall redox balance in tumor cells.

Nanoparticles need to be in the ''right place'' at the ''right rate'' to release drugs or produce redox-active substances to effectively disrupt the redox balance. However, trying to design kinetic-responsive drug delivery systems that respond rapidly to stimuli and have complex mechanisms usually leads to complex drug carrier design and increased difficulty in synthesis.[74] Despite designing nanoparticles as a stimulus-responsive drug delivery system, there are situations where nanoparticles do not respond to stimuli at an optimal rate and extent, resulting in drugs that do not work at the optimal location and time, affecting the precise regulation of the tumor antioxidant system. Studies have reported that it is challenging for exogenous stimulus-responsive materials to penetrate human tissues and accurately reach tumor sites. Endogenous stimuli that can specifically control the release at the tumor site within the appropriate time and dose are also rare.[75] Therefore, the precision of drug release is reduced, and the effect of nanoparticles is weakened.

In conclusion, the ability of nanoparticles to disrupt the redox balance of tumor cells is limited by several factors, and hence the strong antioxidant defenses within tumor cells still resist the drug treatment, resulting in a less than optimal anticancer effect.

3.2.2 Unknown nanopharmacology. Nanomedicine is a rapidly growing field that leverages nano-sized carrier materials for drug delivery. While nanotechnology has vast potential in cancer therapy, its pharmacological mechanisms remain poorly understood and present significant challenges. This uncertainty also applies to nano-ferroptosis therapy.

Research on nanopharmacology focuses on understanding the interaction between drugs and nanomaterials, the systematic pharmacokinetic and pharmacodynamic profiles *in vivo*, and their pharmacological effects in the TME. However, most current anticancer studies have primarily concentrated on the drug profiles, typically neglecting the role of nanomaterials. For instance, in a study by Wu *et al.*, the experiments were specifically designed to examine the toxic side effects of drugs in cancer treatment but did not explore the potential impacts of nanocarriers used.[76] In addition, Su *et al.* investigated the improvement of cancer immunotherapy by chemotherapeutic drug-induced RNA nanoparticles. They demonstrated that chemotherapy-induced tumor RNA nanoparticles (C-RNA-NPs) promoted an immune response in CT-26 colon carcinoma by facilitating DC maturation and increasing T-cell infiltration. However, the study did not further explore the effects of nanomaterials themselves.[77] Similarly, Gao *et al.* developed mesoporous silica-coated gold nanoparticles (AuNCs@mSiO_2) for DOX delivery, revealing the tumor-inhibitory effect of AuNCs@mSiO_2@DOX. However, this study lacked a deeper examination of the nanopharmacological properties of the AuNCs@mSiO_2 nanomaterial.[78]

There are various types of nanocarriers available, each with distinct material genomics, materiomics and nanoarchitectonics. Consequently, their interactions with ferroptosis inducers and pharmacokinetic behavior in the body vary significantly. Mapping these interactions comprehensively is both time-consuming and labor-intensive, and most of them are still in the laboratory exploration stage. Furthermore, studies have shown that certain nanomaterials exhibit potential physiological–pharmacological activities, such as improving the oral bioavailability of chemotherapeutic drugs,[79] enhancing drug stability, controlling drug release,[80] and prolonging the *in vivo* circulation time of drugs.[81] However, how these functions are precisely achieved remains an area in urgent need of comprehensive investigation.

The lack of understanding regarding the pharmacodynamics and pharmacokinetics of chemotherapeutic drug nanoparticles highlights that nanopharmacology is still in a nascent state. The nanopharmacology of nano-ferroptosis therapeutics is also immensely complex and requires in-depth studies to ensure their pharmacokinetic and pharmacodynamic properties align with the needs of clinical applications. In a nutshell, further investigation is essential to elucidate the pharmacological mechanisms of nanomedicines, guide the optimal design of nanomedicines, and ensure their safety and efficacy for clinical administration.

3.2.3 Nanotoxicity risk. Ferroptosis-driven nanotherapies also carry potential risk. On one hand, some ferroptosis inducers or their reaction products can cause damage to non-tumoral tissues or organs. However, this challenge can be mitigated through targeted delivery strategies. On the other hand, the nanomaterials used as delivery carriers may possess inherent cytotoxicity, potentially leading to additional toxic side effects during the administration of ferroptosis inducers.

Nanocarriers are crucial for the efficient and precise delivery of therapeutic drugs, but they may introduce new toxicities. On the one hand, nanocarriers can reduce the side effects of drugs such as ferroptosis inducers through mechanisms such as targeted delivery and controlled drug release. On the other hand, the special physicochemical properties of nanomaterials may also introduce new toxicity risks. The toxicity risk of nanocarriers is closely related to their material composition, surface properties, and size. For example, inorganic nanoparticles may raise certain toxicity concerns. Cerium oxides,[82] carbon nanotubes, and gold, silver, and titanium dioxide nanoparticles[83] can negatively affect several organs (heart, liver, bone marrow, *etc.*), for example by triggering inflammatory reactions, vascular endothelial cell damage, cardiac arrhythmias, and DNA damage. Surface charge will exert some impact. Cationic gold nanospheres have been reported to be toxic at certain doses. Interestingly, gold nanospheres with negatively charged surfaces were found to be non-toxic at the same dose. It was also found that 1.4 nm gold nanorods triggered necrosis, mitochondrial damage and other adverse effects, but 15 nm gold nanorods with the same surface group did not cause cellular damage.[84] Moreover, studies have reported that small-sized nanoparticles may non-specifically penetrate cell membranes, interfering with normal cellular functions and

damaging vital organs due to their relatively large surface area and particle number-to-mass ratio.[85] These indicated the influence of particle size.

Furthermore, ferroptosis induction by specific elements constructing nanocarriers may lead to toxic side effects in normal organs or tissues. In particular, some iron-containing inorganic nanocarriers can induce ferroptosis, and they may also have the potential toxicity mentioned above. For instance, excessive iron accumulation generates free radicals, which can damage cardiac muscle cells, resulting in cardiotoxicity.[86] Additionally, Zhang *et al.* experimentally demonstrated nephrotoxicity during iron accumulation processes. Using arsenic-containing realgar, they observed that it increased iron and ROS accumulation, disrupted the antioxidant system, and induced ferroptosis in a dose-dependent manner, triggering nephrotoxicity in mice.[87] Similarly, manganese (Mn), another trace element, was shown to be neurotoxic when inducing ferroptosis. Wang *et al.* found that Mn exposure increased malondialdehyde, ROS, and ferrous iron accumulation while decreasing GSH and adenosine triphosphate expression. This imbalance resulted in heightened lipid peroxidation, disrupted redox homeostasis, mitochondrial damage, and interference with iron metabolism, ultimately inducing ferroptosis and causing neurotoxicity, as illustrated in Fig. 7.[88]

In summary, while nano-ferroptosis therapy has a pivotal role in advancing oncology, its challenges, such as strong antioxidant systems, addressing gaps in nanopharmacology, and mitigating nanotoxicity risk, cannot be overlooked. It is essential to recognize these limitations and actively pursue innovative solutions to enhance its safety, efficacy, and clinical applicability.

3.3 Opportunities

The opportunities of nano-ferroptosis therapy are vast and promising, encompassing advancements such as AI-based drug screening, the development of nanorobots, and the identification of non-invasive ferroptosis biomarkers. Each of these innovations presents unique potential to overcome current limitations and revolutionize the field, as elaborated below.

3.3.1 AI-based drug screening. Artificial intelligence (AI) has become ubiquitous, transforming various domains, including pharmaceutical sciences. In particular, AI-driven technologies such as machine learning (ML) and deep learning (DL) have played a pivotal role in advancing personalized drug therapy. Among these, DL-based virtual screening harnesses comprehensive information from receptors, ligands, and their interactions to optimize and refine existing compounds.[89] This approach significantly accelerates the process of drug screening, increasing both the speed and success rate of identifying target drugs. Moreover, DL-driven virtual screening facilitates the rapid exclusion of unsuitable drug candidates and the optimization of promising compounds prior to clinical trials, thereby reducing research and development (R&D) timelines, cutting costs, and ultimately contributing to protecting human

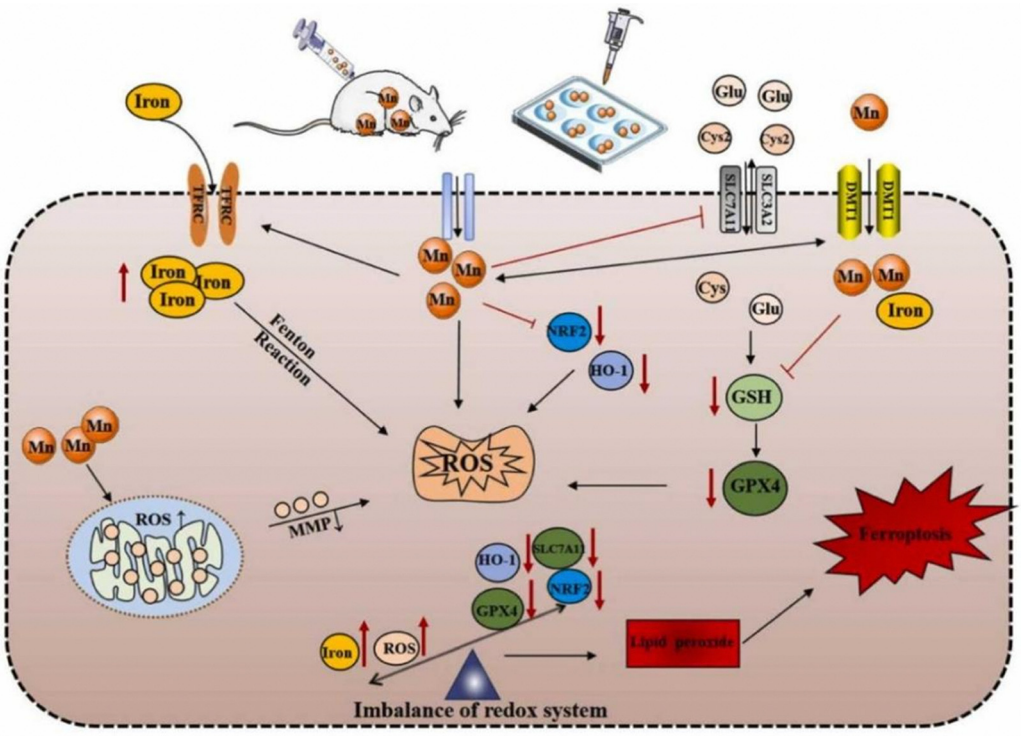

Fig. 7 Neurotoxicity resulting from manganese-induced ferroptosis, driven by iron overload and redox imbalance. Reproduced from Wang *et al.* with permission from Ecotoxicology and Environmental Safety.[88] Abbreviations: Mn: manganese, DMT1: divalent metal transporter protein 1, Glu: glutamate, Cys: cysteine, GSH: glutathione, GPX4: glutathione peroxidase 4, ROS: reactive oxygen species, NRF2: nuclear factor-E2-related factor 2, HO-1: heme oxygenase-1, SLC7A11: solute carrier family 7 member 11, TFR1: transferrin receptor 1, MMP: mitochondrial membrane potential.

health.[90] An example of an application of virtual screening is Insilico Medicine's use of DL and structural biology information to rapidly generate and screen small molecule compounds with high affinity and potential pharmacological activity, INS018_055, through its AI-driven drug design platform Chemistry42. This was the first antifibrotic drug discovered and designed by generative AI and is currently in phase II clinical trials in China and the US.[91] The discovery of this drug sets a precedent for the potential of generative AI to accelerate drug screening, demonstrating the enormous impact of AI in drug development.

AI-based drug screening plays a crucial role in the field of cancer treatment. Kaladharan *et al.* developed an AI-based complex systems response (AI-CSR) smart chip for screening combination therapies, or drug cocktails, for the treatment of CRC. The platform utilized polydimethylsiloxane (PDMS) as a substrate and UV irradiation to form poly(ethylene glycol) diacrylate (PEGDA) hydrogel arrays, enabling precise control over multiple drug dose combinations and their release profiles. Surprisingly, the cocktail drug chip could screen 155 drug dose combinations in just 2.5 hours. The cocktail drug chip required only 1 μL of drug per chip, which greatly reduced the cost of the experiment. The platform provided a new method for drug concentration quantification, enabling rapid, efficient, and accurate drug screening.[92] Similarly, Molyneaux *et al.* successfully identified 76 candidate compounds from a molecular library containing millions of compounds using AtomNet®, a DL-based neural network platform. These compounds were predicted to interact with a newly discovered binding pocket in the protein tyrosine phosphatase mu (PTPmu) structural domain. This binding pocket was located in the groove between the MAM and Ig extracellular structural domains and was essential for PTPmu-mediated cell adhesion.[93] In addition, AI algorithms are powerful tools for the efficient screening and development of nanomedicines in cancer therapy.[94] Dawoud *et al.* screened and optimized lecithin/chitosan nanoparticles using response surface design methodology and successfully identified the best formulation. Subsequently, they also predicted the drug release profiles of the optimized formulation at different time points using an artificial neural network model, and the results demonstrated the high predictive ability of AI for drug release profiles.[95] Additionally, an AI-assisted pharmacokinetic (PBPK) model developed by Chou *et al.* was used to predict the efficiency of tumor-targeted delivery for various NPs. The pharmacokinetic profiles predicted by the AI-PBPK model were highly correlated with experimental measurements of different NPs in the tumor after intravenous injection ($R^2 \geq 0.70$ for 133 out of 288 datasets), demonstrating the efficient and accurate screening capability of AI.[96] Ultimately, this approach facilitates the design of highly efficient, targeted delivery systems to improve cancer therapy outcomes.

In summary, AI-based drug screening holds immense potential in oncological research. By leveraging AI as a screening tool, we can discover *de novo* ferroptosis inducers for nano-ferroptosis therapy in cancer treatment. In addition, AI can be employed to optimize the formulation of nanocarriers, enabling the design of delivery platforms with excellent biocompatibility, favorable degradability, and optimal tumor-targeted delivery efficiency, which are key attributes for developing highly effective cancer therapies.

3.3.2 Nanorobots. Nanorobots are intelligent nanoscale robots that have transformative potential in areas such as targeted drug delivery, biosensing, and diagnostics.[97] Their propulsion mechanisms can be broadly categorized as self-propelled (*e.g.*, using H_2O_2 and enzymes), externally propelled (*e.g.*, using light, acoustic, electric, and magnetic fields), and microbially-propelled (*e.g.*, by bacteria and immune cells). In addition, nanorobots can exhibit triggered release capabilities, responding to specific stimuli such as the physiological environment (*e.g.*, pH), external factors (*e.g.*, light, temperature, and NIR fields), chemical bonding, and mechanical stimuli. One of the most widely studied mechanisms is light-triggered release. By this mechanism, a nanorobot with a photoactive coating absorbs light energy, initiating a photocatalytic reaction to release its payload precisely where needed.[98] These unique and desirable properties position nanorobotics as a promising advancement over traditional carriers, offering significant potential for improving cancer therapeutic delivery.

This highlights the potential of leveraging nanorobotics in nano-ferroptosis therapy for cancers. By integrating nanorobots, we can achieve a more precise, efficient, and safe delivery of therapeutic drugs to the tumor site, minimizing off-target effects and enhancing the overall efficacy of cancer treatment.

3.3.3 Non-invasive ferroptosis biomarkers. Non-invasive biomarker testing is an innovative concept that typically includes serological biomarkers and imaging biomarkers. These biomarkers are used to describe physiological and pathological processes, enabling non-invasive diagnostic imaging and therapeutic decision-making while improving the biocompatibility of diagnostic procedures.[99]

Extensive research has been conducted on ferroptosis markers for disease treatment. For instance, Petrillo *et al.* identified 4-hydroxy-2-nonenal (4-HNE), a lipid peroxidation by-product, along with decreased GSH levels and partial inactivation of glutathione GPX4, as markers of ferroptosis in epilepsy. Elevated NAPDH oxidase 2 (NOX2) expression was also observed, highlighting its role as a significant source of ROS under this condition.[100] These findings suggest NOX2 as a potential ferroptosis biomarker for monitoring the disease progression and assisting in cancer therapy. Similarly, Huang *et al.* demonstrated upregulated levels of farnesyl-diphosphate farnesyltransferase (FDFT1) in response to ferroptosis in renal cell carcinoma (RCC), proposing FDFT1 as a ferroptosis-associated biomarker.[101] In another study, Lyu *et al.* utilized gene set enrichment analysis (GSEA) to highlight fibroblast activation protein-alpha (FAP) as a novel ferroptosis marker in stomach adenocarcinoma (STAD).[102] In conclusion, non-invasive biomarkers offer significant safety in cancer diagnosis and treatment. Developing specialized ferroptosis biomarkers can enable precise monitoring of ferroptosis, predict treatment efficacy, assist in therapy, and enhance the safety and precision of ferroptosis-driven cancer treatment.

The therapeutic potential of ferroptosis nanotherapies in cancer treatment is constrained by several challenges. However, external 'helpers', such as AI drug-based screening models, drug-delivering nanorobots, and the development of non-invasive biomarkers, offer promising solutions. Combining these innovations allows cancer treatment outcomes to be maximized, ensuring more precise, efficient, and safer therapies. Consequently, it is crucial to seize this opportunity to develop cutting-edge cancer treatments that address contemporary needs effectively.

3.4 Threats

Despite the promising potential of nano-ferroptosis therapy, its widespread application faces significant threats, including unsound regulatory mechanisms, challenges in industrial-scale production, and insufficient clinical evidence. These obstacles must be systematically addressed to ensure the effective and safe translation of nano-ferroptosis therapies from research to clinical practice.

3.4.1 Unsound regulatory mechanisms. Regulatory mechanisms of ferroptosis span multiple domains, including genetics, metabolism, and redox homeostasis.[103] While significant progress has been made, our current understanding represents only the tip of the iceberg. The exact regulatory mechanisms of ferroptosis in cancers are complicated and need to be explored in greater depth.

For example, it has been reported that p53 plays an important role in paclitaxel (PTX)-induced ferroptosis by down-regulating SLC7A11 and SLC1A5, though the precise mechanisms remain unclear. The mutational status and cellular context of p53 demonstrated its dual role in ferroptosis. Under conditions of low oxidative stress, p53 exhibits an inhibitory effect on ferroptosis, whereas, under high levels of ROS, it promotes the process. Similarly, heme oxygenase 1 (HO-1) exerts opposing effects on ferroptosis depending on the cellular redox states, acting as both a promoter and an inhibitor. The role of human phosphorylated adenylate-activated protein kinase (AMPK) is equally controversial, with some studies suggesting that AMPK facilitates ferroptosis, while others indicate its activation is associated with ferroptosis resistance. These discrepancies likely reflect differences in specific cellular environments and stress conditions, underscoring the need for further investigation.[104] In addition to these uncertainties regarding the regulatory roles of key molecules, the precise mechanisms by which ferroptosis culminates in cell death remain poorly understood. The peroxidation of PUFA-PLs is recognized as a critical step in ferroptosis, as it impairs membrane function through lipid cross-linking. This process reduces membrane fluidity, ultimately disrupting essential membrane-associated functions and leading to death. However, oxidized PUFA-PLs may produce reactive electrophilic reagents that destroy critical structural and functional proteins within the cell, thereby killing the cell.[105]

However, the lack of a comprehensive understanding of these detailed mechanisms limits the precise application of ferroptosis in anticancer therapies, potentially resulting in suboptimal therapeutic outcomes. Therefore, continuous research is essential to elucidate the intricate processes governing ferroptosis and its regulation in cancer.

3.4.2 Difficulty in industrialization. Despite their advantages in cancer treatment, nano-formulations face significant hurdles in industrial-scale production. Unlike laboratory-scale preparation, the pilot and large-scale productions of nano-formulations are hindered by several factors, including formulation complexity, risks associated with scale-up, quality control challenges, and regulatory approval processes.[106]

The intricate microstructure of nanomedicines, including those incorporating ferroptosis inducers, poses challenges for reproducibility during scale-up production compared with conventional formulations. A prominent issue is the limited applicability of nanometallic catalysts in Fenton-like systems. Suspended powder catalysts, commonly used in laboratory settings, cannot be processed effectively at a large scale and must be converted into effective catalyst modules.[107] Additionally, the scale-up procedures demand the optimization of processing technology and production equipment through rigorous assessments, ensuring strict adherence to regulatory compliance. In this context, quality control poses a significant challenge in the development of nano-formulations. Ensuring the purity, stability, and batch-to-batch consistency of nanomedicines is critical to guaranteeing their safety and efficacy. A key milestone in the industrial translation of nano-formulations is the new drug application (NDA) process, which is both lengthy and rigorous. Strict adherence to relevant regulations at every stage of R&D is essential to meet the quality standards set by domestic and international regulatory agencies. Nevertheless, the absence of clear regulatory guidelines for nano-ferroptosis therapies complicates the R&D process, rendering it partially speculative and associated with considerable uncertainty.

Besides, it has been reported that the development of a pharmaceutical product in the United States can take approximately 12 years and incur costs exceeding $1 billion.[108] It is reasonable to anticipate even higher costs for the development of nano-ferroptosis therapeutics due to their complex nature. Collectively, these factors constitute substantial barriers to the successful industrialization of nano-ferroptosis therapies.

3.4.3 Insufficient clinical evidence. Numerous clinical studies have investigated the application of nanomedicine in cancer treatment (*e.g.*, NCT02033447, NCT00666991, and NCT01103791), leading to successful market launch of products such as doxorubicin liposome, vincristine liposome, and paclitaxel liposome. However, clinical evidence supporting the use of nano-ferroptosis therapies for cancer remains limited. Key challenges include the determination of optimal clinical administration routes, thorough exploration of dosing strategies, the development of advanced clinical testing technologies, and a lack of comprehensive understanding of ferroptosis among clinicians, researchers, and patients.

Nanoformulations can reach the therapeutic site through various clinical administrations, but precise and optimized methods have yet to be developed due to insufficient investigation into the potential issues associated with each route.

For example, oral administration may alter the absorption, distribution, metabolism, or elimination characteristics of the formulation, and the first-pass effects can significantly reduce the bioavailability and potentially cause gastrointestinal side effects or systemic toxicity.[109] Similarly, the injection route requires substantial expertise from healthcare professionals and is associated with side effects such as pain, risk of infection, and local tissue reactions, potentially leading to reduced patient compliance. Transdermal drug delivery may cause skin irritation, allergic reactions such as contact dermatitis, and limited drug absorption due to the barrier posed by the stratum corneum, making it challenging to achieve rapid therapeutic blood concentration.[110] Pulmonary administration may be associated with challenges such as uneven distribution and insufficient accumulation of the therapeutic agents in the lungs, along with risks of respiratory infections or allergic reactions. Additionally, the complexity and high cost of inhalation devices pose significant obstacles.[111] Clinical dosing also needs to be explored in depth. While preclinical studies of nanomedicines have largely relied on animal models, the translation of these findings to clinical settings has been inconsistent. Although specific doses of nanomedicines have shown promising anticancer effects in animal models, these results often fail to replicate in human clinical trials. This discrepancy arises partly because animal models cannot fully simulate human physiology and pathology. On the other hand, nanomedicines may behave differently in humans than in animals.[112] Therefore, the optimal drug doses identified in animal models cannot be simply converted to humans, necessitating more comprehensive studies into interspecies differences. Although ferroptosis occurs in a variety of pathological conditions, current detection methods are mainly limited to *in vitro* experiments and animal models,[113] underscoring the urgent need to develop reliable assays for accurately identifying and quantifying ferroptosis *in vivo*. Finally, as ferroptosis is a relatively novel form of programmed cell death, both researchers and clinical participants may lack a comprehensive understanding of its mechanisms, which hinders the progress of clinical studies. Addressing these challenges through more in-depth exploration is crucial to advancing the clinical application of nano-ferroptosis therapies.

In summary, nano-ferroptosis therapy faces several critical challenges that demand urgent attention, including unsound regulatory mechanisms, difficulty in industrialization, and insufficient clinical evidence. Addressing these threats is essential, requiring the development of robust solutions or alternative strategies to mitigate these risks and ensure the successful translation of this promising therapeutic approach into clinical practice.

4. Development strategies based on SWOT analysis

Based on the SWOT analysis, we have identified the strengths, weaknesses, opportunities, and threats of nano-ferroptosis therapy. To address these aspects, we have constructed a series of development strategies: intensifying strengths, overcoming weaknesses, seizing opportunities, and evading threats. These strategies aim to advance the development and application of nano-ferroptosis therapy in cancer treatment. A concise summary of each strategy is shown in Fig. 8.

4.1 Intensifying strengths

Strategies to enhance the strengths of nano-ferroptosis therapy involve advancing from tissue targeting to subcellular targeting, overcoming chemotherapeutics resistance to apoptosis, and integration of diagnosis and treatment. These strategies will be described in detail in the following sections.

4.1.1 Upgradation from tissue targeting to subcellular targeting. Current targeting strategies primarily focus on organ or tissue level targeting, which only identifies the area where the tumor cells are located. However, different ferroptosis inducers act in specific cellular regions, such as cisplatin and FINO2, which induce ferroptosis in cytoplasm, BQR, RSL5 in mitochondria, and erastin, which significantly induces ER stress to trigger ferroptosis. Therefore, achieving subcellular targeting is crucial for enhancing the precision of anticancer therapy. For example, Liu *et al.* achieved subcellular targeting by delivering DHODH inhibitors to mitochondria in the tumor site through a passive targeting strategy. They synthesized an amphiphilic precursor QA-SS-TPP by functioning the DHODH inhibitor 2-([1,1′-biphenyl]-4-yl)quinoline-4-carboxylic acid (QA) with (4-carboxybutyl)triphenylphosphonium (TPP) *via* a disulfide bond. This precursor spontaneously assembled into an ordered nanostructure QSSP. When QSSP entered the TME, the acidic conditions triggered the breakdown of QSSP, releasing QA and TPP cations driven by mitochondrial membrane potential. This allowed TPP to accumulate at the tumor site and thus target the mitochondria. Meanwhile, the parent drug QA inhibited the mitochondrial anti-ferroptosis defense system, promoting the generation of mitochondrial lipid peroxides and ultimately inducing ferroptosis in cancer cells, thereby facilitating highly effective targeted cancer therapy.[114] In another study, Zhu *et al.* developed carrier-free therapeutic diagnostic ASP NPs through the self-assembly of auriculoside acetate (Aa), scutellaria barbadensis A (SA), and palmitic acid (P). These nanoparticles could induce both mitochondrial apoptosis and ferroptosis in cancer cells, providing synergistic treatment for triple-negative breast cancer (TNBC) with excellent anticancer efficacy.[115] Additionally, the CCM bionic nanoparticle delivery system (EMPP-LOV) developed by Tan *et al.* for the delivery of lovastatin (LOV) targeted the ER and demonstrated enhanced synergistic anti-tumor efficacy.[116] Subcellular targeting offers clear advantages over tissue or organ level targeting, and future advancements may even enable molecular targeting, potentially yielding remarkable anti-cancer results.

4.1.2 Overcoming chemotherapeutics resistance to apoptosis. Several studies have indicated that chemotherapeutic agents such as cisplatin,[117] DOX,[118] and PTX[119] exert their therapeutic effects by inducing apoptosis. However, these agents are often associated with the development of resistance

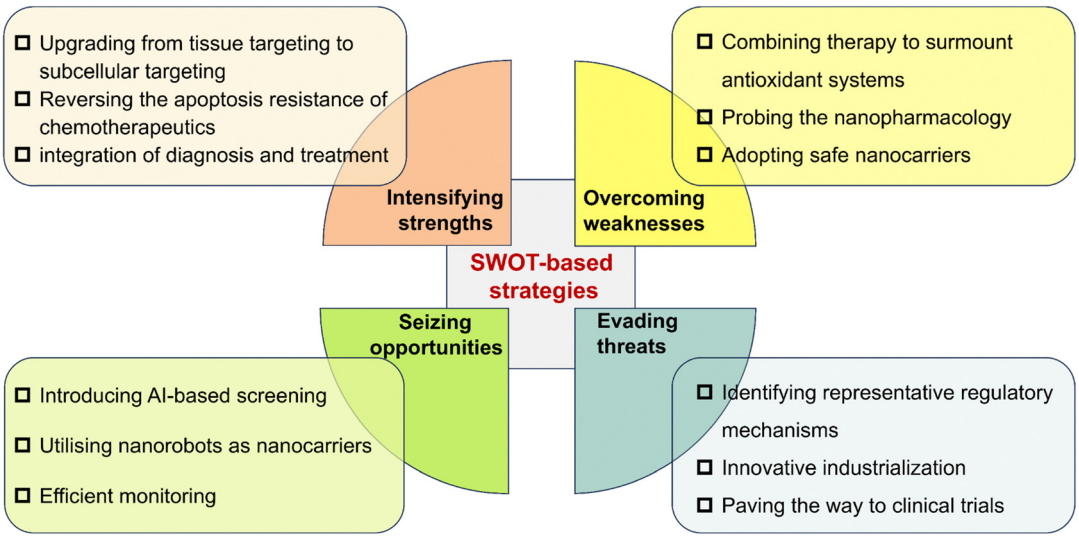

Fig. 8 Development strategies based on SWOT analysis.

in cancer cells. Nano-ferroptosis therapy, by bypassing the conventional apoptosis pathway, offers a promising strategy to counteract this resistance. It is anticipated that the development of nano-ferroptosis/apoptosis bimodal therapies could reduce or even reverse the drug resistance in tumor cells, thereby achieving multiple anti-cancer effects.

For example, Yang *et al.* reported a ferrous metal–organic framework-based nano-agent (FMN) loaded with SLC7A11 siRNA (siSLC7A11) and the chemotherapeutic drug DOX. This nano-agent inhibited intracellular upstream GSH synthesis and induced ferroptosis in cancer cells, reversing chemoresistance and facilitating chemotherapy. The results also demonstrated that FMN overcame the apoptosis-resistant state of cancer cells by regulating the expression of Bcl-2/Bax,[120] thus accelerating cancer cell death. Similarly, Zheng *et al.* used GA–Fe(II)-based liposomal nanosystems loaded with DOX to reverse chemoresistance and induce synergistic ferroptosis/apoptosis. Transcriptomic analysis revealed that ultrasound-enhanced Fenton response downregulated the expression of PGC-1α and Bcl-2, thereby predisposing resistant MCF-7/ADR cells to DOX-induced apoptosis.[121] In addition, Ge *et al.* developed a smart network combining sonodynamic therapy with a nanoenzyme (MoS_2/CF_3SO_2Na nanoparticles, HA@$MoCF_3$ NPs) to reverse cisplatin resistance and enhance ovarian cancer treatment.[122]

Nano-ferroptosis therapy can be combined not only with chemotherapy but also with other therapies to achieve significantly enhanced anticancer effects. For example, Song *et al.* developed a cinnamaldehyde (CA) polymer precursor, PDPCA, for the delivery of all-trans retinoic acid (ATRA), designated as PDPCA@ATRA. They synthesized a pendant CA precursor with an acetal bond in a hydrophobic block, which self-assembled in an aqueous medium. *In vitro* and *in vivo* studies demonstrated that PDPCA@ATRA overcame tumor radioresistance, promoted ferroptosis, and significantly enhanced cytotoxic T-lymphocyte (CTL) responses in lung tumors against PD-1 (αPD-1) immunotherapy.[123] Shi *et al.* designed self-assembled nanomicelles, SANTA FE OXA, which exhibited a comparable effect. The study demonstrated that SANTA FE OXA inhibited tumor growth through a combination of cascade chemotherapy and self-sensitized ferroptosis. In addition, SANTA FE OXA significantly reduced the systemic toxicity typically associated with platinum-based chemotherapy.[124]

4.1.3 Integration of diagnosis and treatment. Nano-ferroptosis therapy utilizes nanoparticles as drug carriers to precisely target tumor cells, minimizing damage to normal tissues and effectively reducing the systemic toxicity of therapeutic drugs. Zhang *et al.* developed transferrin-targeted hollow manganese drug-loaded nanoboxes (hMnTD), which significantly enhanced the immunotherapy efficacy of chemotherapy through a synergistic mechanism of "mitochondrial autophagy-ferroptosis". When hMnTD entered the tumor cells, the high concentration of GSH triggered the degradation of the nanobox and the explosive release of Mn^{2+} and chemotherapeutic drugs. Among them, Mn^{2+} acted as a T_1/T_2 bimodal contrast agent, which enabled real-time visualization of the drug delivery process and changes in the tumor microenvironment, and realized the integration of diagnosis and treatment.[125] Similarly, Qiu *et al.* designed a nano ultrasound contrast agent (arsenic trioxide (ATO)/PFH NPs@Au-cRGD) for efficient ultrasound imaging and liver cancer treatment. Among them, PFH, as an imaging agent for visualizing theranostics, could enhance the ultrasound echo signal while achieving the diagnosis of therapeutic efficacy. The visualization and evaluation of therapeutic efficacy while enhancing anticancer therapy offered great potential for clinical application in liver cancer.[126] Additionally, Wang *et al.* developed smart nanoplatforms (MCMA NPs) for *in situ* release of CO gas loaded with the clinical chemotherapeutic drug mitoxantrone (MTO). Interestingly, the released CO could be used as a contrast agent for ultrasound imaging, combined with fluorescence and photothermal imaging for diagnostic and therapeutic integration, ultimately enhancing anticancer efficacy.[127]

These findings further demonstrated the feasibility of integrating diagnosis and treatment in the process of nano-ferroptosis therapy for cancer treatment to ultimately achieve a better tumor killing effect, which is expected to provide a new strategy for efficient cancer management.

4.2 Overcoming weaknesses

Strategies to overcome the weaknesses of nano-ferroptosis therapy include combining therapy to bypass antioxidant systems, investigating the nanopharmacology in greater depth, and selecting safer nanocarriers. These strategies will be elaborated on in the following sections.

4.2.1 Combination therapy to bypass antioxidant systems. One of the major challenges in ferroptosis is the resistance conferred by the cellular antioxidant defense system. To address this, strategies that disrupt this system could enhance the efficacy of ferroptosis. One promising approach is the combination of ferroptosis and cuproptosis, as both share a common cell death pathway involving mitochondrial damage and are similarly inhibited by GSH. Consequently, their combined therapeutic potential could provide superior cancer treatment, particularly by counteracting the effects of the robust antioxidant system.[128] Nanomaterials with enzyme-like catalytic properties, known as nanoenzymes, play a critical role in facilitating both ferroptosis and cuproptosis. Peroxidase-like (POD-like) nanoenzymes can convert endogenous H_2O_2 to $^{\bullet}OH$, while introducing high-valent transition metal ions such as Fe^{3+} and Cu^{2+} into the nanoenzymes enables them to exhibit GSH peroxidase-like (GPx-like) catalytic ability, thereby reducing GSH levels.[129]

Based on these rationales, Zhang *et al.* developed nanoparticles (O_2^-PFH@CHPI) capable of co-inducing ferroptosis and cuproptosis by loading the photosensitizers indocyanine green (ICG) and O_2^- saturated perfluorohexane (PFH) onto copper-doped hollow Prussian blue (CHP) nanoenzymes. Prussian blue (PB)-based NPs (PB NPs) have strong photothermal conversion properties, making them efficient photothermal agents. Under NIR irradiation, O_2^-PFH@CHPI generate substantial heat due to their high photothermal conversion efficiency, accelerating catalytic reactions. This heat induces the release of O_2, which enhances ICG-mediated PDT, thus promoting cuproptosis and ferroptosis. Simultaneously, an imbalance in intracellular redox homeostasis led to the accumulation of LPO as well as the inactivation of GPX4, further augmenting ferroptosis. Anticancer performance studies revealed that the O_2-PFH@CHPI group exhibited the highest red fluorescence intensity and the lowest green fluorescence intensity, representing the most dead cells and the least viable cells, respectively, compared with the CHP + NIR group. These findings demonstrated that the combined treatment of ferroptosis and cuproptosis enhances the killing effect on cancer cells.[130] Similarly, Li *et al.* reported a nanosystem based on a Cu-tetra(4-carboxyphenyl)porphyrin chloride(Fe(III)) (Cu–TCPP(Fe)) MOF, doped with Au NPs and RSL3, forming anti-cancer nanoparticles Au/Cu–TCPP(Fe). CCK-8 assays showed that the Cu–TCPP(Fe)–PEG group exhibited a modest effect on tumor cell viability, while the Au/Cu–TCPP(Fe)–PEG group exhibited significant inhibition. These results suggest that combination therapy generally inhibited the anti-ferroptosis pathway in tumor cells, amplifying ferroptosis injury and significantly suppressing tumor growth.[131] In addition, the design of core–shell nanoparticles CuP/Er for the co-delivery of copper (Cu) and erastin (Er) to cancer cells demonstrated the potent potential of synergistic cuproptosis and ferroptosis in overcoming the robust intracellular reduction system. The results revealed that the CuP/Er treatment group exhibited a higher tumor growth inhibition (TGI) value (92.3%) compared to the Er–NCP treatment group (52.2%), indicating that the combination of cuproptosis significantly enhances the anticancer effect of ferroptosis.[132]

The combination of ferroptosis and cuproptosis is also referred to as metalloptosis. Studies have shown that, in addition to iron and copper, other metals such as Cd, Mn, Pb, and Zn are also implicated in cancer development.[133] Therefore, metals that are overexpressed in different cancer types could serve as potential targets for anticancer research, offering opportunities for the development of more diverse and targeted cancer therapies.

4.2.2 Probing the nanopharmacology. Nanopharmacology remains poorly understood, which affects the design, development, and clinical efficacy of nanomedicines. Therefore, in-depth research is essential to advance this field. Mastering nanopharmacology is undoubtedly a lengthy and challenging process. To address this, emphasis should be placed on fundamental research, fostering multidisciplinary cooperation, and cultivating specialized expertise.

Exploratory studies on the physicochemical properties of nanomaterials, their interactions with ferroptosis inducers, and their behavior in living organisms, specifically in terms of adsorption, distribution, metabolism, and excretion (ADME), are crucial for advancing nano-ferroptosis therapies. Additionally, the mode of action (MOA) of nano-ferroptosis therapeutics must be thoroughly elucidated. Once the pharmacokinetic and pharmacological profiles are understood, a comprehensive interpretation of nanopharmacology can be achieved. The development of nano-ferroptosis therapy is inherently interdisciplinary, drawing knowledge from fields such as pharmaceutical, material, physical, chemical, and clinical sciences. For example, the impact of physical or chemical surface engineering of the nanocarriers on their response to tumor-specific physiological or pathological signals remains inadequately defined. Collaborative efforts across these diverse scientific domains will be pivotal in uncovering these mechanisms. Therefore, fostering collaborations with researchers from these fields is essential to gain a deeper understanding of nanopharmacology and accelerate the development of nano-ferroptosis therapy. From this standpoint, the cultivation of professionals with multidisciplinary expertise is a key and sustainable strategy for advancing nanopharmacology research.

Therefore, emphasizing fundamental research, fostering multidisciplinary collaboration, and prioritizing professional training represent key strategies elucidating the mechanisms of nanopharmacology, optimizing the design of nanodelivery

systems, and ensuring the safety and efficacy of nano-iron death therapies in clinical treatment.

4.2.3 Adopting safe nanocarriers. To effectively induce ferroptosis in cancer cells, iron-based nanomaterials are frequently employed to supply additional iron as a trigger for ferroptosis. However, iron is a micronutrient and its excessive intake can be harmful. Excessive accumulation of iron can lead to protein and DNA damage, inflammatory reactions, liver cirrhosis, cardiac arrhythmias, and heart failure, among other adverse effects. Therefore, it is crucial to carefully control the amount of iron delivered by the nanocarriers in nano-ferroptosis therapy. Iron-free nanocarriers could represent a more promising alternative.

To minimize carrier toxicity, a two-pronged approach can be adopted. One strategy is to develop self-assembling drugs, while the other involves use of generally recognized as safe (GRAS) materials of natural origin as carriers. Self-assembled nanomedicines, with low or even no addition of carrier materials, can eliminate the biotoxicity associated with nanocarriers and improve biocompatibility.[134] For example, Yue *et al.* developed a co-activated catalytic nano-(CACN) platform by self-assembling DNA-functionalized iron oxide nanoparticles (DNA-FON) and DOX through DNA programming. The results showed that CACN, co-activated by ATP and acidity, exhibited high specificity and efficient ferroptosis to tumors. Furthermore, biocompatibility assays showed that the cell survival and histopathological analysis in the final formulation group were comparable to those of the control group, indicating that the developed nanoplatforms are biocompatible and suitable for *in vivo* therapeutic use.[135] Furthermore, the development of nanocarriers derived from marine natural polysaccharides (such as chitosan and chitin), plant-based materials (such as cellulose and polyphenols), and microbial sources (such as alginate and branched chain starch) presents a promising approach. These materials are known for their excellent biocompatibility, biodegradability, reproducibility, and ease of chemical modification. For example, Xiao *et al.* synthesized nanodroplets (NDs) by conjugating hyaluronic acid (HA) with carboxymethyl chitosan (CMC) through a disulfide-bond (HA–SS–CMC, HSC), and subsequently loaded DOX onto these nanodroplets to form DOX–HSC–NDs. Biosafety assessments showed that the hemolysis rate was less than 5% even at concentrations of HSC–ND as high as 600 μg mL^{-1}, with no pathological changes and no inflammatory reaction in H&E-stained sections of major organs from the HSC–ND-treated group compared to the control group. These results strongly support the superior biocompatibility of the designed NDs as drug delivery carriers, highlighting their potential for further clinical applications.[136] Moreover, Xue *et al.* developed gold nanoclusters (Au–GT) by green chemistry using polyphenols, the main active compounds in green tea extract (GT). They subsequently loaded the anti-tumor drug DOX onto the nanoclusters, creating Au–GT–DOX. The *in vivo* systemic toxicity studies demonstrated that the main organs of mice treated with Au–GT–DOX showed no obvious pathological damage, indicating the excellent biocompatibility of the Au–GT–DOX.[137] Similarly, Ma *et al.* constructed a hydroxyapatite (HAP) nanoscaffold (nHAP@yeasts) inside yeast cells and functionalized it with folic acid (FA) to form a dual-responsive, targeted, long-lasting therapeutic agent. This formulation significantly inhibited cancer cell growth, and the results showed that DOX-nHAP@yeasts-FA significantly reduced the drug-induced damage to normal tissues, demonstrating a favorable safety profile.[138] In summary, the use of self-assembled nanoparticles and naturally derived materials (marine natural polysaccharides, plants, and microorganisms) as carriers offers a powerful strategy for minimizing the toxicity of nano-drug delivery systems.

4.3 Seizing opportunities

Strategies to capitalize on the opportunities presented by nano-ferroptosis therapy primarily involve incorporating AI-based screening, utilizing nanorobots as nanocarriers, and enhancing monitoring techniques. Each of these strategies will be discussed in detail below.

4.3.1 Introducing AI-based screening. AI drug-based screening is an advanced intelligent tool to predict the relationship between drugs and diseases, as well as between diseases and genes. It has the potential to shorten target discovery cycles and reduce research and development costs, making it a valuable asset in cancer treatment. Ferroptosis, a potential target for cancer therapy, can benefit from AI's capabilities to analyze vast compound databases using machine learning and DL algorithms. These technologies enable the rapid identification of optimal drug candidates that induce ferroptosis, while simultaneously improving therapeutic efficacy and minimizing side effects. Furthermore, AI can aid the development and screening of novel small molecule ferroptosis inducers. For example, Zhang *et al.* developed an ML-based disulfidoptosis-related ferroptosis (DRF) scoring system to assess ferroptosis-related features in HCC. The system constructed a scoring model capable of predicting the sensitivity of tumor cells to ferroptosis by analyzing gene expression data related to ferroptosis. The results demonstrated that the model could accurately reflect the sensitivity of cancer cells to ferroptosis inducers, providing a new theoretical basis for the efficient screening of ferroptosis inducers.[139] In addition, a team of researchers recently reported an artificial neural network-based score prediction model for rapid screening of possible ferroptosis inducers in large databases. The results showed that the model can effectively identify potential inhibitors with high affinity for the GPX4 active site from a large database containing 83 catechols and 1024 molecular descriptors, guiding the development and screening of ferroptosis inducers.[140] Similarly, Li *et al.* developed a targeted nanozyme system. They used ML to optimize the composition and structure of the nanozyme to achieve synergistic induction of ferroptosis and apoptosis in tumor cells. The findings demonstrated that the optimized nanozyme system efficiently triggered anti-tumor activity through a sequential response to the TME, thereby initiating a cascade of reactions that lead to ferroptosis.[141] Although challenges remain in terms of drug delivery, tumor specificity, and *in vivo*

circulation duration, the emergence of innovative delivery systems has the potential to mitigate the risks associated with these novel inducers.[142]

We anticipate that advances in computational modeling will continue to drive AI innovations, which will, in turn, facilitate the development of nano-ferroptosis therapy for more effective cancer treatment.

4.3.2 Utilizing nanorobots as nanocarriers. Conventional nanocarriers, such as liposomes, polymeric micelles, and nanogels, often lack the navigational and tissue penetration capabilities essential for smart drug delivery.[143] In contrast, nanorobots offer significant advantages in this regard, as they can be propelled through the body by various mechanisms, enabling precise delivery therapeutics to specific areas, including tumors.

For instance, Li *et al.* developed a DNA nanorobot for targeted delivery of thrombin using DNA origami technology. The M13 phage DNA strand and multiple major strands were co-assembled into a rectangular DNA origami sheet, which was then encapsulated with thrombin on the inside to form a nanodelivery system responsive to nucleolin protein. When an aptamer on the nanorobot binds specifically to nucleolin proteins expressed on tumor-associated endothelial cells, it releases the loaded thrombin, inducing thrombosis within the tumor vasculature and ultimately leading to tumor necrosis. The high biocompatibility of DNA nanorobotics has been demonstrated in both a mouse model with a tumor and a Bama miniature pig model.[144] Similarly, Tang *et al.* designed an enzyme-driven bacterial outer membrane vesicle (OMV) nanorobot for efficient and safe tumor therapy. The use of OMV significantly reduces the toxicity of the delivery system compared to more toxic inorganic nanomaterials. More importantly, the nanorobot employs cell-penetrating peptides to target and penetrate tumors, facilitating the delivery of loaded siRNA while helping it evade enzymatic degradation.[145] These desirable properties of nanorobotics, when compared to traditional carriers, highlight their promising potential in cancer therapeutics.

It is evident that the desirable properties of nanorobots, compared to conventional carriers, offer a promising future for the delivery of cancer therapeutics. These nanorobots can be utilized to specifically deliver drugs, including ferroptosis inducers, thereby advancing the development of nano-ferroptosis therapy in cancer treatment.

4.3.3 Efficient monitoring. The development of non-invasive biomarkers for ferroptosis plays a crucial role in diagnostic imaging and therapeutic decision-making in nano-ferroptosis therapy for cancers. Efficient monitoring can be achieved by detecting the expression levels of ferroptosis-related biomarkers to evaluate the therapeutic effect, rather than the cumbersome task of quantifying the effective concentration of the therapeutic drugs. This approach is especially appropriate for ferroptosis inducers with a narrow, individualized, or variable therapeutic window.

In the previous section, we demonstrated that NOX2, RSP7, FDFT1, and FAP could serve as ferroptosis biomarkers. The techniques to determine these biomarkers are summarized as follows. Yue *et al.* developed a GSH/APE1 cascade-activated therapeutic nanoplatform (GAN) to counteract apurinic/apyrimidinic endonuclease 1 (APE1), a protein that induces therapeutic resistance (''ferroptosis resistance''). They employed a 7T-MRI animal imaging system and a fluorescence imaging system to monitor ferroptosis activation, APE1 expression, and drug release *in vivo*. The results showed that this adaptive imaging and therapeutic nanoplatform provided switchable magnetic resonance imaging (MRI) and dual-channel fluorescence signals while delivering synergistic therapy mediated by GSH/APE1-activated LPO. Therefore, it can be used to monitor ferroptosis activation and therapeutic resistance processes *in vivo*, leading to highly specific and efficient ferroptosis-based anticancer therapy.[146] Similarly, Huang *et al.* developed a homotypic cancer cell membrane-camouflaged iron small interfering RNA mimetic nanohybrid (CM-Fe-siR) to design an integrated nanoplatform that combines tumor targeting, monitoring, and ferroptosis-based therapeutic treatment for cancer. The authors monitored the onset of ferroptosis *in vivo* using MRI and fluorescence imaging. The results demonstrated that the platform effectively triggered sustainable ferroptosis through multiple synergistic effects, significantly enhancing anticancer efficacy.[147] Moreover, Liu *et al.* reported the use of small-sized upconversion nanoparticles (UCNPs) coated with mesoporous SiO_2 as the nanocarrier to load dual drugs, MnO_2 and MRI, for hypoxic tumor theranostics. In this study, the authors employed UCL imaging to track the *in vivo* distribution of UPSMF/MB, and the results indicated that UPSMF/MB significantly enhanced the ferroptosis-mediated killing effect, leading to substantial tumor growth inhibition.[148] We anticipate further advances in analytical chemistry and biochemistry to expand the range of biomarker assays, which will accelerate the development of nano-ferroptosis therapy.

4.4 Evading crisis

Strategies to address the challenges of nano-ferroptosis therapy include identifying representative regulatory mechanisms, fostering innovative industrialization, and facilitating the transition to clinical trials. These strategies will be elaborated upon in the following sections.

4.4.1 Identifying representative regulatory mechanisms. The precise regulatory mechanisms underlying ferroptosis are still under investigation, which may impact the application of nano-ferroptosis therapy for cancer treatment.

However, while exhaustive mechanisms are being identified, it is possible to bypass the uncertainties in this ''danger zone'' by focusing on the most well-established and representative pathways. The major theories regarding the mechanisms of ferroptosis include the following: ferroptosis is characterized by the accumulation of intracellular LPO and damage to the cell membrane. An imbalance in the intracellular antioxidant system, particularly in the transport of cystine into the cell and its reduction to cysteine *via* the system Xc^- (composed of SLC7A11 and SLC3A2) system, is closely related to the initiation of ferroptosis. In addition, disruptions in iron metabolism are

crucial; when iron homeostasis is impaired, excess iron accumulates within cancer cells, producing highly toxic •OH through the Fenton reaction. These radicals can react directly with PUFA, generating large amounts of lipid ROS that ultimately lead to cell death. Various organelles, including mitochondria, lysosomes, and the endoplasmic reticulum, play a role in regulating ferroptosis by influencing iron accumulation, lipid synthesis, and lipid peroxidation. Dysfunction in these organelles can alter cellular sensitivity to ferroptosis.

Among these mechanisms, the accumulation of LPO is the most widely studied and is recognized as the central event. Investigating this aspect in greater detail may provide valuable insights into enhancing nano-ferroptosis therapy. For example, LPO can be detected using different techniques, including LPO assay kits, gas chromatography-mass spectrometry (GC-MS),[149] and fluorescent probes such as BODIPY.[150] The measurement of LPO levels can, in turn, reflect the progression of ferroptosis.

4.4.2 Innovative industrialization. We can strategically address the challenges encountered in the industrialization of nano-ferroptosis therapeutics. Firstly, the issue of formulation complexity in nanoformulations can be simplified through modular design computer models, optimization of synthesis pathways, and reduction of formulation components.[151] Secondly, the reproducibility of nanoformulations can be enhanced by developing innovative techniques to rapidly screen for a minimal yet optimal formulation composition.[152] Moreover, to mitigate the risks associated with pilot amplification, detailed engineering calculations and simulations can be performed on pilot equipment. Automated control systems, capable of monitoring and adjusting reaction temperature, pressure, flow rate, and other key parameters in real-time,[153] can be integrated to ensure the safety and efficacy of the product. Moreover, optimized production processes, such as microfluidics, can streamline manufacturing, increasing the feasibility of scaling scale-up to pilot production.[154] In addition, for quality control concerns, a robust quality control system should be implemented to test raw materials, intermediate products, and final products across multiple batches and items. The pilot process should include comprehensive quality record-keeping and analysis, enabling the monitoring of product quality. This ensures timely adjustments to process parameters or operational methods, maintaining the stability and consistency of product quality.[155] Finally, addressing administrative approval issues requires a thorough review of regulatory matters related to industrial transformation projects. This includes understanding relevant policy documents, industry standards, and the specific processes involved in drug registration and approval.[156] Proactive preparation and continuous monitoring of the latest guidelines and internal regulations will help facilitate approval processes. Strict adherence to regulatory requirements during product R&D is essential to ensuring a smooth transition from administration approval to the market launch.

In conclusion, the potential challenges of nano-ferroptosis therapy can be mitigated by simplifying prescriptions, implementing strategies to facilitate large-scale production, establishing a robust quality control system, and collecting relevant information to plan accordingly.

4.4.3 Paving the way to clinical trials. To identify accurate and safe clinical routes of administration for nanoformulations, in-depth research on the target drug should be conducted prior to clinical trials. Key factors to consider include the physicochemical and pharmacological properties of the formulations, such as particle size, surface charge, solubility,[157] stability in different environments,[158] therapeutic range,[159] and speed of onset.[160] The surface charge of the nanoformulations significantly influences its interaction with the biofilm.[161] For instance, positively charged nanoformulations may bind more strongly to negatively charged biofilms, which can impact the choice of route of administration. Similarly, for drugs that require rapid action and broad distribution (*e.g.*, targeting cancer cells throughout the body), intravenous injection is typically the preferred route, as it enables quickly entry into the bloodstream.[162] Additionally, in preclinical studies, the side effects of nanoformulations across various routes of administration should be thoroughly and comprehensively evaluated. Every effort should be made to identify the safest and most effective administration routes.

In terms of determining the optimal drug dosage clinical use, extensive animal model studies can be leveraged, and the data should be verified and optimized through computer simulation and human body modeling techniques.[163] This approach aims to replicate the human body's response as closely as possible, ultimately facilitating the clinical translation of nanomedicines.

The occurrence of ferroptosis is associated with changes in both biochemical properties and cellular morphology.[164] By synthesizing these signals, researchers can develop novel clinical detection techniques for ferroptosis,[165] thereby providing strong support for clinical diagnosis and treatment.

Specialized training courses on ferroptosis must be organized for relevant personnel prior to clinical trials. For example, experts or senior researchers in the field can be invited to share practical research cases, ensuring a robust knowledge domain. Furthermore, an internal knowledge database on ferroptosis should be established, detailing detection indexes, reference ranges for different disease models, and the advantages and disadvantages of different detection methods. This will ensure safe and efficient clinical operations.

We propose the establishment of a data-sharing platform to facilitate global collaboration between researchers and clinicians, thereby accelerating the accumulation of clinical evidence for nano-ferroptosis therapy.

5. Conclusion and outlooks

Emerging nano-ferroptosis therapies represent promising approaches for cancer treatment. This review began by providing an overview of the current state of research on nano-ferroptosis therapy across various cancer types, then focusing on four key aspects of this therapy: strengths (tumor targeting, mitigating drug resistance, and reducing drug side effects),

weaknesses (the uncertain ability of nanoparticles to disrupt redox balance, undefined nanopharmacology, and potential nanotoxicity risk), opportunities (AI-based drug screening, nanorobots, and non-invasive ferroptosis biomarkers), and threats (uncertain regulatory mechanisms, difficulties in industrialization, and insufficient clinical evidence). Furthermore, we proposed development strategies to address both the strengths and limitations of nano-ferroptosis therapy, including advancements from tissue targeting to subcellular targeting, overcoming apoptosis resistance in chemotherapeutics, integration of diagnosis and treatment, combination therapies to surmount antioxidant systems, further investigation into nanopharmacology, and the adoption of safe nanocarriers. Additionally, we emphasized the integration of AI-based screening, the use of nanorobots as nanocarriers, and the importance of efficient monitoring, along with identifying representative regulatory mechanisms, advancing industrialization, and paving the way for clinical trials. It is anticipated that this review will provide valuable insights for the development of innovative and effective cancer treatment strategies, further advancing the fields of nanomedicine and ferroptosis therapies.

In light of the opportunities and challenges faced by nano-ferroptosis therapy, it is important to recognize that we are at a pivotal juncture in the development of this kind of therapy. With continuous research and progress in nanotechnology and ferroptosis mechanisms, it is expected that several nano-ferroptosis therapies will advance into clinical practice, providing safer and more effective treatment options for cancer patients.

Author contributions

Conceptualization, Zhengwei Huang; writing – original draft, Qian Chen and Junli Zhu; writing – review & editing, Qian Chen; supervision, Zhengwei Huang and Junhuang Jiang; funding acquisition, Zhengwei Huang.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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